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EXAMINER	
SULLIVAN, DANIEL M	

ART UNIT	PAPER NUMBER
1636	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/619,939	DRAGHIA-AKLI ET AL.	
	Examiner	Art Unit	
	Daniel M. Sullivan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-37* is/are pending in the application.

4a) Of the above claim(s) *21-23,25-28,30 and 31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20 and 24* is/are rejected.

7)☒ Claim(s) *29* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *15 July 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7/04, 11/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This is the First Office Action on the Merits of the application filed 15 July 2003, which claims benefit of US provisional application 60/396,247 filed 16 July 2002. Claims 1-37, as originally filed are pending.

Election/Restrictions

Applicant's election without traverse of Group I, claims 1-31, and the species SEQ ID NO: 7 and SEQ ID NO: 19 in the reply filed on 27 June 2006 is acknowledged.

Claims 32-37 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention and claims 21-23, 25-28, 30 and 31 are withdrawn from further consideration as being drawn to nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in the 27 June reply.

Claims 1-20, 24 and 29 are presently under consideration.

Specification

The disclosure is objected to because of the following informalities:

The specification contains sequence that is not identified by SEQ ID NO (e.g., brief description of Figures 3, 5, 6, 7, 9, 10, 11, 13, 14, 15, 21, 22 and 23; p. 27, between ¶¶0084-0085). Furthermore, the use of SeqID# throughout the specification is improper. The proper abbreviation is "SEQ ID NO".

> "Where the description or claims of a patent application discuss a sequence that is set forth in the 'Sequence Listing' in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the sequence identifier, preceded by 'SEQ ID NO:' in the text of the description or claims,

even if the sequence is also embedded in the text of the description or claims of the patent application" 37 C.F.R. 1.821(d).

Appropriate correction is required.

Claim Objections

Claims 4, 6, 8, 10, 13, 14, 24 and 29 are objected to because of the following informalities: The claims use the improper abbreviation "SeqID#" in referring to the nucleic acid sequence listing. *Id.*

Claim 1 is objected to because the word "polyadenylation" is misspelled in part (c).

Claim 19 is objected to because the claim ends with two periods.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-17, 19 and 20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a synthetic mammalian expression plasmid utilized for plasmid mediated gene supplementation, wherein the plasmid comprises a nucleic acid encoding GHRH, does not reasonably provide enablement for any synthetic mammalian expression plasmid having the features recited in the claims and useful for plasmid mediated gene supplementation. The specification does not enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (a) the nature of the invention; (b) the breadth of the claims; (c) the state of the prior art; (d) the amount of direction provided by the inventor; (e) the existence of working examples; (f) the relative skill of those in the art; (g) whether the quantity of experimentation needed to make or use the invention based on the content of the disclosure is "undue"; and (h) the level of predictability in the art (MPEP 2164.01 (a)).

Nature of the invention and Breadth of the claims: The instant claims are directed to a mammalian expression plasmid comprising a synthetic or eukaryotic promoter, a codon optimized eukaryotic therapeutic gene sequence, a polyadenylation signal, a selectable marker gene, a ribosomal binding site, a selectable marker gene sequence and an origin of replication. The claim further recites, "the synthetic mammalian expression plasmid is utilized for plasmid mediated gene supplementation".

MPEP 2164.01(c) states: "When a compound or composition claim is limited by a particular use, enablement of that claim should be evaluated based on that limitation. See *In re Vaeck*, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991)." As the instant claims recite that the claimed invention is utilized for plasmid mediated gene supplementation, enablement is evaluated based on that intended use. Thus, the enabling specification must teach the skilled artisan how to make a plasmid suitable for plasmid gene supplementation wherein the plasmid

comprises any synthetic or eukaryotic promoter operably linked to any eukaryotic therapeutic gene sequence in accordance with the broadly generic scope of what is claimed.

State of the prior art and level of predictability in the art: Although the art provides evidence that myogenic expression of GHRH can be used in gene supplementation (see, e.g., Draghia-Akli et al. (1999) *Nature Biotechnol.* 17:1179-1183 and Draghia-Akli et al. (1997) *Nature Biotechnol.* 15:1285-1289; each of which was made of record in the IDS filed 14 November 2003), the art of gene supplementation is highly unpredictable and evidence of enablement for an single "eukaryotic therapeutic gene sequence" cannot be taken as evidence that gene supplementation is enabled for any "eukaryotic therapeutic gene sequence".

In particular, at the time of filing, *in vivo* gene therapy utilizing the direct administration of recombinant nucleic acids, regardless of the mode of delivery (*e.g.,* adenovirus, retrovirus, liposome), was considered to be highly unpredictable. Verma et al. states that, "[t]he Achilles heel of gene therapy is gene delivery...", and that, "most of the approaches suffer from poor efficiency of delivery and transient expression of the gene" (Verma et al. (1997) *Nature* Volume 389, page 239, column 3, paragraph 2). Marshall concurs, stating that, "difficulties in getting genes transferred efficiently to target cells—and getting them expressed—remain a nagging problem for the entire field", and that, "many problems must be solved before gene therapy will be useful for more than the rare application" (Marshall (1995) *Science*, Vol. 269, page 1054, column 3, paragraph 2, and page 1055, column 1).

Orkin *et al.* further states in a report to the NIH that, "... none of the available vector systems is entirely satisfactory, and many of the perceived advantages of vector systems have not been experimentally validated", and that, "[w]hile the expectations and the promise of gene

therapy are great, clinical efficacy has not been definitively demonstrated at this time in any gene therapy protocol" (Orkin *et al.* (1995) Report and recommendations of the panel to assess the NIH investment in research on gene therapy, page 1, paragraph 3, and page 8, paragraph 2).

Numerous factors complicate the gene therapy art which have not been shown to be overcome by routine experimentation. Eck *et al.* (1996) Goodman & Gilman's The Pharmacological Basis of Therapeutics, 9th Edition, Chapter 5, McGraw-Hill, NY, explains, "the delivery of exogenous DNA and its processing by target cells require the introduction of new pharmakokinetic paradigms beyond those that describe the conventional medicines in use today". Eck *et al.* teaches that with *in vivo* gene transfer, one must account for the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced. These factors differ dramatically based on the vector used, the protein being produced, and the disease being treated (see Eck *et al.* bridging pages 81-82).

Also among the many factors that the art teaches affect efficient gene delivery and sustained gene expression are, immune responses and the identity of the promoter used to drive gene expression. Verma et al. teaches that weak promoters produce only low levels of protein, and that only by using appropriate enhancer-promoter combinations can sustained levels of therapeutically effective protein expression be achieved (Verma et al., *supra*, page 240, column

2). Verma et al. further warns that, "...the search for such combinations is a case of trial and error for a given type of cell" (Verma et al., *supra*, page 240, bridging sentence of columns 2-3). The state of the art is such that no correlation exists between successful expression of a gene and a therapeutic result (Ross *et al. Human gene Therapy*, vol. 7, pages 1781-1790, September 1996, see page 1789, column 1, first paragraph).

In an article published near the effective filing date of the instant application, Rubanyi (2001) *Mol. Aspects Med.* 22:113-142 teaches that the problems described above remained unsolved at the time the instant application was filed. Rubanyi states, "[a]lthough the theoretical advantages of [human gene therapy] are undisputable, so far [human gene therapy] has not delivered the promised results: convincing clinical efficacy could not be demonstrated yet in most of the trials conducted so far..." (page 113, paragraph 1). Among the technical hurdles that Rubanyi teaches remain to be overcome are problems with gene delivery vectors and improvement in gene expression control systems (see especially "**3. Technical hurdles to be overcome in the future**", beginning on page 116 and continued through page 125).

Beyond the technical barriers common to all gene therapy approaches, each disease to be treated using gene therapy presents a unique set of challenges that must be addressed individually. Rubanyi teaches, "each disease indication has its specific technical hurdles to overcome before gene therapy can become successful in the clinic" (page 131, third full paragraph). Rubanyi states, "the most promising areas for gene therapy today are hemophilias, for monogenic diseases, and cardiovascular disease (more specifically, therapeutic angiogenesis for myocardial ischemia and peripheral vascular disease...) among multigenic diseases" (page 113, fourth paragraph). As of the filing date of the instant application, however, even these most

promising areas presented barriers to successful gene therapy that could not be traversed by routine experimentation.

With regard to hemophilia, Schwaab *et al.* (2001) *Semin. Thromb. Hemost.* 27:417-424 teach that immune response against gene therapeutically administered Factor VIII and Factor IX compromised the success of therapy in many animal studies and that, "the situation is still more complicated by the fact that hemophilia B-affected dogs that have been intravenously treated with canine Factor IX protein without immune response against canine Factor IX develop antibodies when treated by gene therapy" (page 421, first paragraph in column II). Schwaab *et al.* also affirms that gene delivery remains a substantial problem in the development of gene therapy for hemophilia (see especially the second paragraph in column 2 on page 421). In subsequent discussion of ongoing clinical trials of gene therapy for hemophilia A and B, Schwaab *et al.* teach that, as of 2001, the effectiveness of gene therapy as a treatment for hemophilia had not been established (see beginning the final paragraph on page 421 and continued through the first paragraph of the second column on page 422). These teachings demonstrate that, as of the time of filing, successful treatment of hemophilia using gene therapy was unpredictable regardless of the delivery method employed.

With regard to gene therapy of ischemia, Rissanen *et al.* (2001) *Eur. J. Clin. Invest.* 31:651-666, teaches that although applications of therapeutic angiogenesis for ischemic disorders has established the proof of principle that exogenous growth factors can augment circulatory defects in animals and man, many important questions remain to be addressed. "Firstly, mechanisms of collateral growth by exogenous growth factors are still unclear...[a]dditional factors...may be required for collateral formation and maintenance of functional blood vessels.

Secondly, the persistence of new vessels is unknown after transient gene expression. Thirdly, improvement is needed in gene transfer efficiency..." (paragraph bridging pages 659 and 660). Emanueli *et al.* (2001) 133 :951-958 further teach that, "[d]elivery of angiogenic inducers...in ischaemic tissues allows rescue of blood perfusion. However, angiographic studies clearly show that the newly formed vasculature is abnormal and not well organized as in normal tissues...resembling the characteristics of leaky haemangiomas..." (page 955, the paragraph bridging columns 1 and 2). These teachings show that, even in an area of gene therapy considered promising, significant obstacles to successful therapy remained well after the effective filing date of the instant application.

Further evidence of the disparate obstacles encountered in developing a vector suitable for gene supplementation is found in the teachings of MacColl et al. (1999) *J. Endocinol.* 162:1-9. For example, MacColl et al. teaches that treatment of erythropoietin insufficiency by gene supplementation requires that the production of Epo be properly regulated so as to avoid overproduction of erythrocytes. (See especially the ¶ bridging pp. 3-4). MacColl et al. further teaches that overproduction of decorin in order to suppress TGFβ production in the treatment of glomerulonephritis also requires specificity that is not presently available. (See especially p. 4, ¶2.) Finally, MacColl et al. teaches that the impact of VEGF on the immune system and on the maturation of dendritic cells is a factor that must be considered in developing useful gene supplementation.

Viewed as a whole, the teachings of Rubanyi, Schwaab et al., Rissanen et al. and MacColl et al. clearly evidence that the use of expression plasmids for gene supplementation is

highly unpredictable and critical factors such as effective dosage and route of administration must be determined empirically for each therapeutic gene sequence.

Amount of direction provided by the inventor and existence of working examples: With regard to gene supplementation, the teachings of the instant application are directed almost exclusively to the GHRH gene. The specification states, "The delivery of specific genes to somatic tissue in a manner that can correct inborn or acquired deficiencies and imbalances has been demonstrated in the prior art." (¶0063.) However, the specification provides no specific examples of correction of inborn or acquired deficiencies and imbalances.

The specification teaches: "By utilizing codon optimization, essential bacterial structural elements (e.g., bacterial antibiotic resistant genes) are synthetically constructed and used to replace codons that contained detrimental sequences, but do not effect [sic] the final gene product" (¶0067); various expression vectors and promoters routinely used in the art (see especially ¶¶0068-0069, ¶¶0071-0074) as well as other common vector components (see especially ¶¶0075-0083). The specification also teaches the construction of an optimized plasmid backbone and optimized GHRH molecules (Examples 1 and 2). However, the specification provides no teachings that would enable the skilled artisan to overcome the obstacles identified in the prior art cited above such that the skilled artisan would be able to use any synthetic mammalian expression plasmid within the scope of the claims for plasmid mediated gene supplementation as recited in the claims.

Relative skill of those in the art and quantity of experimentation needed to make or use the invention: Although the level of skill in the art is high, given the high degree of unpredictability in the relevant art, the skilled artisan would not be able to make and use the full

scope of what is claimed according to the claim limitations without engaging in undue experimentation. The art clearly teaches that obtaining useful gene supplementation using any given therapeutic gene sequence is highly unpredictable. The "predictability or lack thereof" in the art refers to the ability of one skilled in the art to extrapolate the disclosed or known results to the claimed invention. If one skilled in the art can readily anticipate the effect of a change within the subject matter to which the claimed invention pertains, then there is predictability in the art. On the other hand, if one skilled in the art cannot readily anticipate the effect of a change within the subject matter to which that claimed invention pertains, then there is lack of predictability in the art. Accordingly, what is known in the art provides evidence as to the question of predictability.

In the instant case, the art evidences that useful gene supplementation was not routinely practiced in the art at the time of filing and, given that each therapeutic gene sequence and gene supplementation protocol presents unique challenges, enablement for any given mammalian expression plasmid construct for use in gene supplementation cannot be predictably extrapolated to gene supplementation using other therapeutic gene sequences. As the teachings of the instant disclosure provide no guidance that would enable the skilled artisan to use any eukaryotic therapeutic gene sequence for plasmid gene sequence other than GHRH, making and using what is claimed beyond the scope of a mammalian expression vector comprising a nucleic acid encoding GHRH would require undue experimentation. Therefore, the claims are properly rejected under 35 USC §112, first paragraph, as lacking enablement for the full scope of the claimed subject matter.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-20 and 24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-20 are indefinite in being directed to a synthetic mammalian expression plasmid comprising "a codon-optimized-eukaryotic therapeutic gene sequence". The specification defines "optimized codon" at ¶0055 as "a codon that has a match codon frequencies [sic] in target and host organisms, but does not alter the amino acid sequence of the original translated protein." As an optimized codon is any codon that matches the codon frequencies in a target or host organism and the codon frequencies vary among host organisms, the limitation is relative, depending upon the host organism being considered. In view of this, any given codon might be considered "optimized" with respect to one host organism and "not optimized" with respect to another organism. In other words, the same nucleic acid sequence might be considered within the scope of the claims based on the codon frequency in one organism and outside of the claimed invention based on the codon frequency in another organism. Therefore, it is not possible to determine the metes and bounds of the clamed subject matter unless the claim clearly identifies the host organism upon which "codon optimization" is based.

Claim 1 is indefinite in reciting, "selectable marker gene promoter" in part (d). The phrase might be understood as requiring that the promoter be linked to a selectable marker gene such that the promoter drives expression of the selectable marker, as requiring that the promoter occur naturally in a gene that is used as a selectable marker (e.g., the LacZ promoter) but need

not drive expression of a selectable marker in the construct, or that the promoter might be any promoter with the capacity to drive expression of a marker gene sequence (i.e., any promoter). As the specification provides no definition of a "selectable marker gene promoter" and each of the possible alternative interpretations of the claim limitation are of substantially different scope, the limitation renders indefinite the scope of the claim as a whole.

Claims 2-20 and 24 are indefinite insofar as they depend from claim 1.

Claims 15, 16, 18 and 24 are further indefinite in reciting, "the codon optimized mammalian therapeutic gene sequence". There is no antecedent basis for the limitation "mammalian therapeutic gene sequence" in claim 1, which recites "eukaryotic therapeutic gene sequence". Claim 16 is further indefinite insofar as it depends from claim 15.

Claim Construction

Office personnel are to give claims their broadest reasonable interpretation in light of the supporting disclosure. *In re Morris*, 127 F.3d 1048, 1054-55, 44 USPQ2d 1023, 1027-28 (Fed. Cir. 1997).

As discussed above, the limitation "codon optimized" is indefinite in the absence of an identified host organism upon which optimization is based. Given the ambiguity of the limitation "codon-optimized", the "codon-optimized-eukaryotic therapeutic gene sequence" of the claims is construed as reading on essentially any eukaryotic therapeutic gene sequence because any coding sequence would comprise one or more codons that match the codon frequency in one or more host organisms (e.g., the codon frequency of the native host organism).

Claim Rejections - 35 USC § 102

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 2, 5, 7-9, 11 and 14-20 are rejected under 35 U.S.C. 102(b) as being anticipated by Draghia-Akli et al. (1997) *Nature Biotechnol.* 15:1285-1289 (made of record in the IDS filed 14 November 2003) as evidenced by the attached plasmid map for pBS (available at www.stratagene.com/vectors/maps/pdf/pbs.gif).

Independent claim 1 is directed to a synthetic mammalian expression plasmid comprising (a) a synthetic or eukaryotic promoter; (b) a codon-optimized-eukaryotic therapeutic gene sequence; (c) a polyadenylation signal; (d) a selectable marker gene promoter; (e) a ribosomal binding site; (f) a selectable marker gene sequence; and (g) an origin of replication, wherein elements (a), (b) and (c) are operably linked and located in a first operatively linked arrangements and elements (d), (e), (f) and (g)are operably linked and located in a second operatively linked arrangement.

Draghia-Akli et al. teaches a synthetic mammalian expression plasmid (pSK-GHRH; see especially p. 1288, ¶4) comprising a first operably linked arrangement comprising a eukaryotic promoter (i.e., avian skeletal muscle α-actin promoter) fused to a fragment of the human GHRH cDNA comprising part of exon 2, all of exon 3 and part of exon 4 and encoding the 31 amino acid signal peptide and the mature hGHRH 1-44, which constitutes a codon-optimized-eukaryotic therapeutic gene sequence according to the broadest reasonable interpretation thereof

(Id.), and the 3' untranslated region of the human growth hormone cDNA, which, absent evidence to the contrary, comprises a polyadenylation signal. Furthermore, the pSK-GHRH plasmid of Draghia-Akli et al. comprises a second operably linked arrangement comprising a kanamycin antibiotic resistance gene for bacterial selection. As the selectable marker gene must be expressed in bacteria in order to function, the selectable marker necessarily comprises a selectable marker gene promoter and a site for ribosome binding so that the encoded protein can be translated. Finally, Draghia-Akli et al. teaches that pSK-GHRH plasmid was derived from pBS, which comprises the ColE1 origin of replication.

Thus, the pSK-GHRH plasmid of Draghia-Akli et al. comprises each of the elements of the synthetic mammalian expression plasmid of the instant claim 1. Furthermore, the pSK-GHRH plasmid comprises the elements recited in dependent claims 2, 5, 7-9, 11 and 14-20. The ColE1 origin of replication is a prokaryotic origin of replication according to claim 2; the RBS comprises a prokaryotic RBS (evidenced by the fact that the kanamycin gene is expressed in prokaryotic cells) according to claim 5; and the polyA signal is eukaryotic (i.e., human) according to claim 7. Furthermore, in view of the fact that SEQ ID NO: 10 is identified as the hGH polyadenylation signal (see, e.g., the sequence listing) and the pSK-GHRH vector comprises the hGH 3' UT region, the skilled artisan would conclude that the pSK-GHRH polyadenylation signal comprises SEQ ID NO: 10 according to claim 8, absent evidence to the contrary.

Claim 9 requires that the vector comprise 5' UTR that is a portion of a eukaryotic 5' UTR. Given that the specification provides no limiting definition of "a portion", the limitation is reasonably construed as encompassing any single nucleotide that might be found in a eukaryotic

5' UTR (i.e., a, g, c, or t). The pSK-GHRH vector clearly comprises multiple portions of a eukaryotic 5' UTR.

As discussed above, the pSK-GHRH comprises a selectable marker gene that is expressed in prokaryotic cells which necessarily comprises a prokaryotic promoter according to the limitations of claim 11.

Claim 15 requires that the codon optimized mammalian therapeutic gene sequence comprise at least one species specific codon modification. The specification provides no definition of a "species specific codon modification". The broadest reasonable interpretation of the claim limitation is that the codon optimized mammalian therapeutic gene sequence is produced by a process in which at least one species-specific codon is modified. As such, the codon optimized mammalian therapeutic gene sequence of the claim is viewed as product defined by the process of its production.

Determination of the patentability of a product-by-process claim is based on the identity of the product, not its method of production. If the product in the product-by-process claim is the same (or obvious) from a product of the prior art, the claim is unpatentable, even if the product was made by a different process. *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985). When assessing patentability, the product-by-process claim has potential patentability when the manufacturing steps impart identifiable, distinctive structural characteristic to the final product. In the instant case, given the ambiguity of what constitutes a codon optimized sequence and the fact that essentially all codons can be construed as optimized in the absence of a clearly identified reference organism, any coding sequence can be considered to comprise one or more optimized codons. What is more, an optimized codon is the same regardless of whether that

codon was modified relative to some other sequence, which in the instant case is also undefined, or is present in unmodified form. Therefore, the recitation that the mammalian therapeutic gene sequence comprises at least one species specific codon modification does not distinguish the claimed invention from the pSK-GHRH vector of Draghia-Akli et al.

The mammalian therapeutic gene sequence in the vector of Draghia-Akli et al. encodes a 31 amino acid hGHRH signal peptide according to claim 16, which is specific to human according to claim 17, and further encodes a species specific (i.e., human) GHRH according to claim 18 and 5' untranslated sequence according to claim 19 (i.e., all eukaryotic RNAs comprise some untranslated sequence 5' to the translational start site for ribosome binding). Finally, with regard to claim 20, as discussed above, the specification provides no limiting definition of what constitutes a "portion" of a nucleic acid sequence and therefore the limitation is construed as broadly encompassing any single nucleotide found in the reference sequence. In view of this construction, the 5' untranslated sequence of Draghia-Akli et al. meets the limitations of claim 20.

The synthetic mammalian expression plasmid of Draghia-Akli et al. comprises all of the elements of the claimed invention; therefore, the claims are anticipated by Draghia-Akli et al.

Claims 1, 2, 5, 7-9, 11 and 14-20 are rejected under 35 U.S.C. 102(e) as being anticipated by Schwartz et al. US Patent No. 6,423,693 (made of record in the IDS filed 12 July 2004; hereinafter Schwartz '693) as evidenced by Draghia-Akli et al. (*supra*) and the attached plasmid map for pBS (*supra*).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Schwartz '693 discloses the plasmid vector pSK-GHRH as an exemplary preferred embodiment of the invention claimed therein, which is the same as the pSK-GHRH plasmid described in Draghia-Akli et al. (See especially col. 10, ll. 23-25 and col. 23, ¶2 of Schwartz '693) As the vector of Schwartz et al. is the same as the vector of Draghia-Akli et al. the claims are anticipated by Schwartz '693 for the reasons stated herein above. It is further noted that, although not required to anticipate the claims as presently written, Schwartz '693 does explicitly teach embodiments wherein the GHRH sequence is codon optimized. (See especially col. 9, ll. 19-30).

Claims 1-9 and 11-20 are rejected under 35 U.S.C. 102(e) as being anticipated by Schwartz et al. US Patent No. 6,551,996 (made of record in the IDS filed 14 November 2003; hereinafter Schwartz '996).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the

inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

The limitations of the instant claim 1 and the interpretation of the claim limitations in light of the disclosure is discussed herein above. In Example 1, commencing at page 26, the instant specification describes the construction of an optimized plasmid backbone using as the starting material the plasmid pSP-HV-GHRH having the backbone pAV0125, which the disclosure teaches was described in US Patent No. 6,551,996 (i.e., Schwartz '996). (See especially ¶0084). The instant application summarizes the changes made in the pAV0125 plasmid of Schwartz '996 in ¶0088 and in ¶0089 teaches the elements comprised by the product vector pAV0201. Based on this description, it can be inferred that the pAV0125[1] vector of Schwartz '996 comprises the following elements: the hGH poly A signal, the c5-12 synthetic eukaryotic promoter; the pNEO prokaryotic promoter and a transposon fragment ("Tn5'); one NEO ribosome binding site; and a pUC18 origin of replication. Furthermore, Schwartz '996 teaches that the pSP-HV-GHRH vector comprises an optimized GHRH coding sequence. (See especially Examples 2 and 8.) Thus, in view of the evidence of record, the skilled artisan would conclude that the pSP-HV-GHRH vector of comprises each of the elements recited in claims 1-9 and 11-20. It is noted that, although Schwartz '996 does not disclose specific sequence for the pUC18 ori (claim 4), the RBS (claim 6), the hGH polyA sequence (claim 8), the PNEO promoter (claim 13) or kanamycin gene (claim 14), given that the working example in the instant case was derived from the vector of Schwartz '996, it is presumed, absent evidence to the contrary, that

[1] It should be noted that Schwartz '996 does not explicitly refer to a vector pAV0125, but does disclose the plasmid pSP-HV-GHRH (see, e.g., Example 8), which the instant application teaches comprises the pAV0125 backbone.

the sequence of the elements recited in the instant claims is the same as the sequence of those same elements in the pSP-HV-GHRH vector of Schwartz '996.

Finally, although it does not appear that the pSP-HV-GHRH plasmid comprises an ARS as recited in claim 3, Schwartz '996 teaches at col. 13, ll. 28-28 that the vectors contemplated therein might comprise an ARS as an alternative to an origin of replication.

In view of the foregoing, the skilled artisan would conclude that the vector of Schwartz '996 is the same as the vector of the instant claims. Therefore, the claims are anticipated by Schwartz '996.

Claims 1-9 and 11-20 are rejected under 35 U.S.C. 102(b) as being anticipated by Schwartz et al. (February 2001) WO 01/06988 (hereinafter Schwartz '988) as evidenced by Schwartz et al. '996 (*supra*).

The disclosure of Schwartz '988, at least with respect to the working examples, appears to be identical to the disclosure of Schwartz et al. '996. Therefore, for the reasons stated herein above with regard to anticipation of the claims under 35 USC §102(e) by Schwartz et al. '996, the claims are also anticipated under 35 USC §102(b) as anticipated by Schwartz et al. '988.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference

claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

An obviousness-type double patenting rejection is appropriate where the conflicting claims are not patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would be obvious over, the reference claim(s). The MPEP states, at §804,

> The specification can always be used as a dictionary to learn the meaning of a term in the patent claim. *In re Boylan*, 392 F.2d 1017, 157 USPQ 370 (CCPA 1968). Further, those portions of the specification which provide support for the patent claims may also be examined and considered when addressing the issue of whether a claim in the application defines an obvious variation of an invention claimed in the patent. *In re Vogel*, 422 F.2d 438, 441-42, 164 USPQ 619, 622 (CCPA 1970). The court in *Vogel* recognized "that it is most difficult, if not meaningless, to try to say what is or is not an obvious variation of a claim," but that one can judge whether or not the invention claimed in an application is an obvious variation of an embodiment disclosed in the patent which provides support for the patent claim. According to the court, one must first " determine how much of the patent disclosure pertains to the invention claimed in the patent" because only "[t]his portion of the specification supports the patent claims and may be considered." The court pointed out that "this use of the disclosure is not in contravention of the cases forbidding its use as prior art, nor is it applying the patent as a reference under 103, since only the disclosure of the invention claimed in the patent may be examined."

Claims 1, 2, 5, 7-9, 11 and 14-20 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-14 of U.S. Patent No. 6,423,693 (Schwartz '693; *supra*) as evidenced by Draghia-Akli et al. (*supra*) and the attached plasmid

map for pBS (*supra*). Although the conflicting claims are not identical, they are not patentably distinct from each other.

The limitations of the instant claims are recited herein above. Claim 1 of Schwartz '693 is directed to a vector comprising a cassette comprising a nucleotide sequence encoding a codon optimized GHRH (i.e., SEQ ID NO: 2; see especially col. 9, ll. 19-30); a 5' flanking region including a promoter; and a 3' flanking region comprising 3' UTR. Claim 2-4 of Schwartz '693 recite that the construct comprises various eukaryotic promoters, claim 6 of Schwartz '693 recites that the construct comprises 3' UTR from a hGH gene and claim 14 recites that the construct comprises an antibiotic resistance gene.

The claims of Schwartz et al. do not explicitly recite that the construct comprises a poly adenylation signal, a selectable marker gene promoter, a ribosomal binding site or an origin of replication. However, each of these elements can be found in the disclosed preferred embodiments of the invention. In particular, the specification discloses the plasmid vector pSK-GHRH or a plasmid comprising a nucleotide sequence which is the same as the sequence of pSK-GHRH as an exemplary preferred embodiment of the invention. (See especially col. 10, ll. 23-25 and col. 23, ¶2 of Schwartz '693.) As the vector of Schwartz et al. is the same as the vector of Draghia-Akli et al. (Id.), for the reasons set forth herein above regarding anticipation of the instant claims by the teachings of Draghia-Akli et al., the limitations of the instant claims are found in the "exemplary preferred embodiment" disclosed in Schwartz '693. As the elements of the pSK-GHRH plasmid are disclosed as preferred, it is clear that the elements are within the scope of the invention claimed in Schwartz '693 and their inclusion would be obvious in view of the preferred status of the pSK plasmid. It is further noted that Schwartz '693 also includes

explicit teachings that the vector might comprise a polyA signal (col. 9, ¶1), and teaches each of the elements recited in the instant claims as part of the pSK-GHRH vector at col. 22, ¶6.

In view of the foregoing, the skilled artisan would conclude that the instant claims are not patentably distinct from the claims of Schwartz '693. Therefore, the claims are properly rejected under the judicially created doctrine of obviousness double patenting.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M Sullivan whose telephone number is 571-272-0779. The examiner can normally be reached on Monday through Friday 6:30-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

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